GUIDANCE[1]

GLIPIZIDE

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Glipizide is an oral antidiabetic agent which lowers blood glucose levels. It is used as an adjunct to diet for the management of non-insulin-dependent diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet alone. Although the precise mechanism of hypoglycemic action of glipizide has not been clearly established, the drug appears to lower blood glucose concentration mainly by stimulating release of endogenous insulin from beta cells of the pancreas (1).

To achieve maximum reduction in postprandial blood glucose concentration, glipizide should be administered 30 minutes before a meal. The recommended initial adult dose of glipizide is 5 mg daily and the maximum recommended once daily dose is 15 mg. Optimum dosing regimen of glipizide for each patient is obtained by titration. Glucose (urinary and blood) and blood glycosylated hemoglobin (Hb A1c) should be used as the indicators of effective therapy (1). The most commonly

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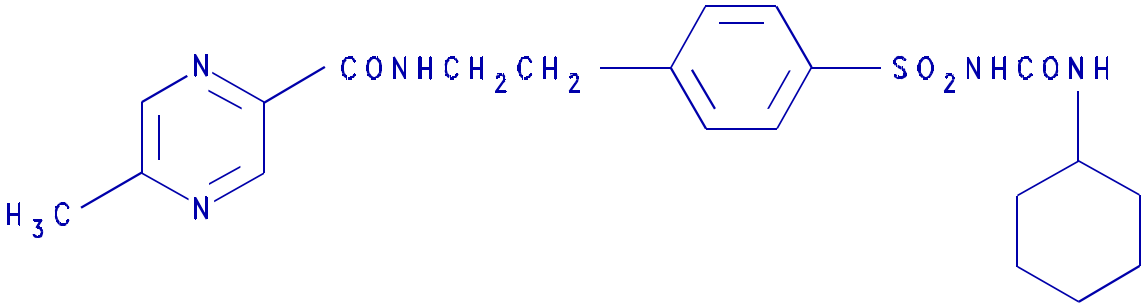
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

observed adverse effects of glipizide are dizziness, sweating, tremors and lightheadedness (1,2).

The drug is currently marketed as immediate release tablets, 5 mg and 10 mg, by Roerig Division of Pfizer Inc. under the brand name Glucotrol ^{R} (1,3).

B. Chemistry

Glipizide is a sulfonylurea and antidiabetic agent which is structurally similar to acetohexamide and glyburide (1,4). The drug is a whitish powder which is practically insoluble in water and alcohols. It has a molecular weight of 445.55 and pKa of 5.9 (1). The structural formula of glipizide is shown below :



C. Pharmacokinetics

Glipizide is rapidly and completely absorbed after oral administration with a bioavailability of approximately 95% (1,5). After oral administration, the drug is 98.4% bound to plasma proteins (5), reaches C_{max} in 1 to 3 hours (1,2), has an elimination half-life of 2 to 5 hours (1,2,5,6), and volume of distribution (Vd) of 11 L (1,7). From the mean plasma profiles, glipizide appears to have either single compartment disposition or a very short distribution phase (2,8). Primary metabolites (1,7) of glipizide are hydroxylation products and polar conjugates that are inactive and are excreted in both urine (70%) and feces. Biliary excretion is estimated to be approximately 30%. Less than 5 - 10% of the administered drug is excreted intact in urine (1,5). Extent of absorption of an oral dose of glipizide is unaffected by food in normal

volunteers but the absorption is delayed by about 40 minutes (1). There are conflicting reports about the influence of food on Tmax (2). Plasma glipizide levels of 20 to 90 ng/ml have been reported to be therapeutically effective (9).

II. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

A. Product Information

1. FDA Designated Reference Product: 10 mg Glucotrol[R] Tablet (Roerig).

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger .

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Types of Studies Required

1. A single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting condition comparing equal doses of the test and reference products.

2. A single-dose, randomized, three-treatment, three-period, six-sequence, crossover, limited food effects study comparing equal doses of the test under fasting condition as well as the test and reference products when administered immediately following a standard breakfast.

C. Recommended Protocol for Conducting a Single Dose, Bioequivalence Study under Fasting Condition

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[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given in equal labeled doses.

Design (Single Dose): The study design is a single dose, two-treatment, two-period, two-sequence crossover with a one week washout period between Phase I and Phase II dosing. Equal numbers of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers aged 18 to 50 years and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

Procedures (Single Dose)[3]*:* Following an overnight fast of at least 10 hours, subjects should be administered a single dose (1x10 mg tablet) of the test or reference product with 240 ml 20% glucose solution in water. Subjects should receive 60 ml of 20% glucose solution in water every 15 minutes after dosing for 4 hours.

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[3] Glipizide (5 and 10 mg) and glyburide (1.25, 2.5, and 5 mg), the second generation sulfonylurea antidiabetic agents, are comparatively more potent than tolbutamide (250 and 500 mg) and tolazamide (100, 250 and 500 mg). Therefore, in a fasting bioequivalence study involving normal subjects, hypoglycemic events occur more frequently with glipizide and glyburide than with tolbutamide and tolazamide (2). Moreover, in the case of glipizide, the hypoglycemic episodes in normal subjects participating in a fasting bioequivalence study were fewer when the glucose was given to subjects every 15 minutes than when it was given every 30 minutes (2). In a study with such a design, measurement of plasma glucose is not necessary because it will not reflect the pharmacodynamic end point. However, such design is preferable to the usual fasting study design to ensure the welfare of subjects and to avoid excessive drop out rate.

Restrictions: Study volunteers should be subject to the following restrictions:

a. No additional water or other fluids (except for that described above for drug dosing) are allowed from 1 hour predose to 1 hour postdose .

b. Except for glucose administration, subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx medication beginning two weeks and OTC drug beginning one week before drug administration until after the study is completed.

Blood Sampling (Single Dose): Venous blood samples should be collected pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours post-dose. Plasma should be separated promptly and immediately frozen until assayed. Following a one week washout period, subjects should begin Study Phase Two.

Analytical Methods: The active ingredient should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, accuracy, and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and quality control chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data (Plasma): See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design."

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

D. Limited Food Effects Study

The limited food effects study should be performed in the same manner as the single-dose fasting study, with the following exceptions:

Procedures: Equal number of subjects should be assigned to each of the six dosing sequences possible in a three-treatment, three-period study design. Each subject will receive the following treatments:

Treatment 1: Generic Product, [1x10 mg tablet] administered after a standard breakfast [4]

Treatment 2: Reference (Glucotrol [R]) Product, [1x10 mg Tablet] administered after a standard breakfast [4]

Treatment 3: Generic Product, [1x10 mg Tablet] administered in the fasting state.

Following a ten hour fast, the subjects receiving the treatments under fed condition should be served a standard breakfast [3]. The subjects should have thirty minutes to finish the entire breakfast, and then be immediately dosed with Treatment 1 or 2, with 240 ml of 20% glucose solution in water. Subjects receiving the treatment under fasting condition should receive Treatment 3, with 240 ml 20% glucose solution in water. The lots of the test and reference products used in this limited food effect study should be the same as the lots used in the fasting study, above. Every

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[4] Each subject should consume a standardized, high fat content meal consisting of:

One buttered English muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes
Eight fluid oz. (240 mL) of whole milk
Six fluid oz. (180 mL) of orange juice

subject (in all three Treatments) should be given 60 ml of 20% glucose solution in water, post dose, every 15 minutes for four hours. No food should be allowed for at least 4 hours post-dose, and no additional water or fluids should be allowed from 1 hour predose to 1 hour postdose. Subjects should be served scheduled standardized meals throughout the study.

Statistical Analysis: In general, no food effect will be assumed if the AUC_{0-T}, $AUC_{0-\infty}$, and C_{max} mean values for the generic product administered under fed condition (Treatment 1) are within 20% of the respective mean values for the reference product administered under fed condition (Treatment 2).

Retention of Samples: The laboratory conducting the bioequivalence testing should retain an appropriately identified reserve sample of the test product and the reference standard used to perform the *in vivo* bioequivalence study for the approval of the application. Each reserve sample should consist of at least 200 dosage units. For more information please refer to CFR 21, 320.32.

III. *IN VITRO* TESTING REQUIREMENTS

There is currently no official monograph on glipizide drug products in USP XXII, and there is thus no USP dissolution testing method. A tentative method recommended by FDA is described below.

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test and reference products. Wherever applicable, the lots of the dosage units used in the *in vitro* dissolution testing should be the same as the lots of the dosage units used in the *in vivo* bioequivalence study. The following method and tolerances are recommended:

Apparatus:	USP XII apparatus 2 (paddle)
RPM:	50
Medium:	SIF (without enzyme) pH 7.5
Volume:	900 ml
Sampling Times:	15, 30, 45 and 60 minutes
Tolerance (Q):	NLT 80% in 45 minutes

Analytical: Validated method

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

IV. WAIVER REQUIREMENTS

A. Waiver of *in vivo* bioequivalence study requirements for the 5 mg tablet of the generic product may be granted as per 21 CFR 320.22(d)(2), provided both of the following conditions are met:

1. The 5 mg tablet is proportionally similar in both active and inactive ingredients to the 10 mg tablet that has been shown *in vivo* to be bioequivalent to the listed reference product.

2. The 5 mg tablet of the generic product meets the *in vitro* dissolution testing requirements.

V. REFERENCES

1. Physician's Desk Reference. 46th ed. Montvale, NJ: Medical Economics Company, 1992:1952-4.

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8. Wahlin-Boll E, Almer LO, Melander A. Bioavailability, pharmacokinetics and effect of glipizide in type 2 diabetics. Clin Pharmacokinet 1982;7:363-72.

9. Groop LC, Barzilai N, Ratheiser K, Luzi L, Wahlin-Boll E, Melander A, DeFronzo RA. Dose-dependent effect of glyburide on insulin secretion and glucose uptake in Humans. Diabetes Care 1991;14(8):724-7.

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